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Scientific Article

Hypofractionated image guided radiation therapy followed by prostate seed implant boost for men with newly diagnosed intermediate and high risk adenocarcinoma of the prostate: Preliminary results of a phase 2 prospective study

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Abstract

Purpose: A phase 2 protocol was designed and implemented to assess the toxicity and efficacy of hypofractionated image guided intensity modulated radiation therapy (IG-IMRT) combined with low-dose rate ^{103}Pd prostate seed implant for treatment of localized intermediate- and high-risk adenocarcinoma of the prostate.

Methods and materials: This is a report of an interim analysis on 24 patients enrolled on an institutional review board–approved phase 2 single-institution study of patients with intermediate- and high-risk adenocarcinoma of the prostate. The median pretreatment prostate-specific antigen level was 8.15 ng/mL. The median Gleason score was 4 + 3 = 7 (range, 3 + 4 = 7 - 4 + 4 = 8), and the median T stage was T2a. Of the 24 patients, 4 (17%) were high-risk patients as defined by the National Comprehensive Cancer Network criteria, version 2016. The treatment consisted of 2465 cGy in 493 cGy/fraction of IG-IMRT to the prostate and seminal vesicles. This was followed by a ^{103}Pd transperineal prostate implant boost (prescribed dose to 90% of the prostate volume of 100 Gy) using intraoperative planning. Five patients received neoadjuvant, concurrent, and adjuvant androgen deprivation therapy.

Results: The median follow-up was 18 months (range, 1-42 months). The median nadir prostate-specific antigen was 0.5 ng/mL and time to nadir was 16 months. There was 1 biochemical failure associated with distant metastatic disease without local failure. Toxicity (acute or late) higher than grade 3 was not observed. There was a single instance of late grade 3 genitourinary toxicity secondary to hematuria 2 years and 7 months after radiation treatment. There were no other grade 3 gastrointestinal or genitourinary toxicities.

Conflicts of interest: None.

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Conclusions: Early results on the toxicity and efficacy of the combination of hypofractionated IG-IMRT and low-dose-rate brachytherapy boost are favorable. Longer follow-up is needed to confirm safety and effectiveness.

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Introduction

Conventional treatment options for patients with localized intermediate- to high-risk adenocarcinoma of the prostate include radical prostatectomy, external beam radiation therapy (EBRT), interstitial brachytherapy with or without EBRT, and expectant management.[1] Patients with higher risk disease may be treated with androgen deprivation therapy (ADT) in the neoadjuvant, concurrent, and oftentimes adjuvant setting.

Dose escalation with radiation therapy has been associated with improved biochemical outcomes.[2-5] The concern with dose escalation is the potential for increased normal tissue toxicities. EBRT using image guided intensity modulated radiation therapy (IG-IMRT) in combination with prostate seed implant boost has been used in the setting of dose escalation while attempting to minimize normal tissue toxicity.[6] Low-dose-rate (LDR) prostate seed implant allows for a conformal dose delivery over several months. EBRT with IG-IMRT provides dose to the prostate capsule, seminal vesicles with a margin of 5 to 8 mm, an area at risk for disease spread that is not routinely covered by brachytherapy alone.[6]

The typical dose of radiation therapy delivered in combination with seed implant is 4500 cGy of IMRT in 25 fractions. This regimen is generally well-tolerated and effective, and the National Comprehensive Cancer Network (NCCN) guidelines also recommends this treatment option for intermediate- and high-risk cancers.[7-17] However, a drawback for patients is the 5-week duration of IMRT, which is time-consuming, relatively expensive, and can be logistically prohibitive for some patients.

Because of advances in imaging and IMRT technology, improved treatment precision is possible, allowing for safe delivery of hypofractionated doses of radiation therapy. Several studies have demonstrated that the alpha-beta ratio for prostate cancer may be as low as 1 to 3 Gy, reflecting the slow proliferation rate of prostate cancer.[7,18-22] In addition, the alpha-beta ratio does not alter significantly with the diagnostic risk level.[23] It is proposed that, because the alpha-beta ratio of prostate cancer appears to be similar to or lower than the surrounding normal tissues, there may be an increased therapeutic ratio with higher doses per fraction.[24] Current radiation therapy treatment regimens using moderately hypofractionated radiation therapy for prostate cancer in randomized trials typically deliver IMRT in 240 to 400 cGy/fraction over 4 to 6 weeks.[25-31] These moderately hypofractionated regimens have been reported to have similar toxicity and effectiveness compared with conventional IMRT (180-200 cGy/fraction).[17] More recently, studies have assessed "extreme" hypofractionation (500-725 cGy/fraction) using stereotactic body radiation therapy (SBRT) for ≤5 days of treatment. Single institution series have showed similar efficacy and safety when compared with conventional treatment.[32-37] In addition, a pooled analysis of prospective phase 2 clinical trials showed the 5-year biochemical relapse free survival rate of 95%, 84%, and 81% for low-, intermediate-, and high-risk patients, respectively.[38] A systematic review of SBRT reported that this technique is more cost-effective compared with conventionally fractionated IMRT.[39] At this time, the NCCN guidelines recommend that hypofractionation using SBRT be considered a cautious alternative in clinics with the technology, physics, and clinical expertise.[17]

The current study is designed to evaluate the tolerability and efficacy of a 5-day course of image-guided IMRT with a dose biologically equivalent to 4500 cGy in 25 fractions, followed by a Pd-103 implant. To our knowledge this is the first study adding LDR prostate seed implant boost to hypofractionated IMRT to improve the radiobiologic therapeutic ratio while maintaining reasonable patient convenience and reducing cost.

Methods and Materials

Patient selection

The eligibility criteria for the study included patients at least 18 years of age with a Zubrod Performance Scale 0 to 1 and locally confined adenocarcinoma of the prostate with the following characteristics: clinical stages T1c-T2b (American Joint Committee on Cancer, 6th Edition); prostate-specific antigen (PSA) <10 combined Gleason score ≥7; PSA >10 combined Gleason score ≥6; maximum PSA ≤20. In addition, the patients had to have no significant obstructive symptoms (goal American Urological Association [AUA] scores ≤15), a pre-implant prostate volume of ≤60 mL by transrectal ultrasound, and

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